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CLINICAL CASE SEMINAR

Adrenocortical-Pituitary Hybrid Tumor Causing Cushing's Syndrome

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ABSTRACT

We describe the first case of an adrenocortical-pituitary hybrid tumor causing Cushing's syndrome in a 17-yr-old boy. Adrenal vein sampling confirmed elevated secretion of both cortisol and ACTH precursors from a right adrenal mass, whereas pituitary ACTH levels, as determined by bilateral inferior petrosal sinus samples (IPSS), were unresponsive to CRH and equal to peripheral levels. There was no biochemical or histological evidence for a pheochromocytoma, but, rather, the tumor demonstrated lipid-rich clear cells characteristic of an adrenocortical adenoma. Immunohistochemical analysis revealed ACTH immunoreactivity and synaptophysin proteins in the tumor. Isolation of tumor cells by the novel technique of laser capture microdissection and subsequent RT-PCR showed expression of POMC messenger ribonucleic acid and cytochrome p450 enzyme messenger ribonucleic acid within the same cells. Finally, ultrastructural analysis provided ultimate proof for adrenocortical-pituitary hybrid cells exhibiting the characteristic vesicular mitochondria and abundant smooth endoplasmic reticulum of steroid cells and the typical secretory granules of corticotrophs within the cytoplasm of the same cells. The adrenocortical tumor expressed the pituitary transcription factor pituitary homeobox factor 1 and the steroidogenic factor 1. The intermingling of the centrally located ectodermally derived pituitary tissue with the mesodermally derived adrenocortical tissue in this adenoma suggests a hitherto unrecognized genetic and phenotypic plasticity within the hypothalamic-pituitary-adrenal axis. (*J Clin Endocrinol Metab* **86:** 2631–2637, 2001)

CUSHING'S SYNDROME can be ACTH dependent, most commonly due to a pituitary corticotroph tumor or ectopic ACTH production, or ACTH independent, due to adrenocortical, cortisol-producing tumors (1–3). Here we present an unusual case that challenges this classification and our views on tumor development in the hypothalamic-pituitary-adrenal (HPA) axis. We report an adrenal tumor containing both pituitary and adrenal elements that produced Cushing's syndrome. Adrenal vein sampling suggested the secretion of both cortisol and ACTH from a right adrenal mass, whereas ACTH levels in the inferior petrosal sinuses were equal to peripheral levels. There was no imaging, biochemical, or histological evidence of a pheochromocytoma; in fact, the tumor was comprised of lipid-rich clear cells, characteristic of an adrenocortical adenoma. Immunohistochemical analysis revealed the presence of ACTH immunoreactivity and synaptophysin in the tumor. Isolation of tumor cells by laser capture microdissection and subsequent RT-PCR showed expression of POMC, 17α-hydroxylase, and pituitary homeobox factor-1 messenger ribonucleic acid (mRNA) within the same cells. Finally, ultrastructural analysis provided ultimate proof that there were adrenocortical-pituitary hybrid cells exhibiting both the characteristic vesicular mitochondria and abundant smooth endoplasmic reticulum (SER) of steroid-secreting cells in addition to the typical secretory granules of corticotrophs.

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Case Report

A 17-yr-old boy presented with a 1-yr history of hypertension, swelling of the extremities, increasing obesity, facial plethora and fullness, easy bruising, and abdominal enlargement with development of large purple striae. Physical examination revealed weight of 70 kg, height of 162.7 cm, and blood pressure of 151/99 mm Hg. Cushingoid features included facial plethora, bilateral supraclavicular fat pads and a dorsocervical fat pad, truncal obesity, and multiple violaceous striae on his abdomen, thighs, and axillae. The patient did not present with signs of hyperpigmentation.

Plasma cortisol concentrations were elevated, with loss of circadian rhythm [19.5 μg/dL (538 nmol/L) at midnight; 21.3 μg/dL (587 nmol/L) at 0730 h]. Mean 24-h urinary free cortisol excretion was elevated at 399 μg. Plasma ACTH values were persistently elevated, ranging from 29.0 pg/mL (6.42 pmol/L) to 63.5 pg/mL [14.1 pmol/L; normal range, 0–23 pg/mL (0–5.1 pmol/L)]. There was failure of suppression of morning cortisol after administration of 8 mg dexamethasone at midnight and a lack of response for ACTH after iv administration of 1 mg/kg ovine CRH. Coronal and sagittal sections (3 mm) through the pituitary using Tesla magnetic resonance imaging (MRI) did not show any abnormality.

An MRI scan of the neck, chest, and abdomen and a computed tomography scan of the chest and pelvis failed to reveal a source of ectopic ACTH.

An adrenal CT scan revealed a 3-cm round mass with calcification and central necrosis and/or fat attached to the medial limb of the right adrenal gland. The remainder of the right gland and the left gland appeared atrophic, consistent with an ACTH-independent process. T2-weighted MRI of the adrenals was not suggestive of a pheochromocytoma. Plasma and urinary catecholamine and metanephrine levels were normal. There was no response to a glucagon stimulation test.

Bilateral adrenal venous sampling revealed cortisol production from the right adrenal gland (553 μg/dL; 15,257 nmol/L), which responded to exogenous ACTH (3,150 μg/dL; 86,908 nmol/L). Cortisol levels in the left adrenal vein (29.9 μg/dL; 824 nmol/L) were similar to peripheral levels (15 μg/dL; 413 nmol/L) and did not respond to ACTH (21 μg/dL; 579 nmol/L). Right adrenal vein samples contained ACTH (24 ng/L; 5.3 pmol/L) and large amounts of ACTH precursors (1,091 pmol/L).

The patient underwent laparoscopic right adrenalectomy. Postoperative cortisol and ACTH values were undetectable, necessitating hydrocortisone replacement. The clinical stigmata of Cushing's syndrome resolved gradually.

Materials and Methods

Molecular and histological evaluation

Tissue from the patient's tumor and from four cortisol-producing adenomas from other patients with ACTH-independent Cushing's syndrome was transferred to tubes containing prechilled PBS (pH 7.6) and kept on ice until immunohistochemical and molecular studies were performed. Three tumors from patients with adrenocortical carcinoma, three pheochromocytomas, and three pituitary corticotroph adenomas were studied in parallel along with normal human adrenal glands and pituitaries from four patients who underwent nephrectomy for renal carcinoma or at autopsy. Approval of the use of human tissues for research was obtained by the corresponding committee on the protection of the rights of human subjects from each participating institute.

Assays

For all measurements, 8 mL blood were taken into a chilled syringe with ethylenediamine tetraacetate and immediately centrifuged at 1600 $\times$ *g* for 15 min at 4 C. Plasma was stored at −70 C until analysis. ACTH [normal range, 0–23 pg/mL (0–5.1 pmol/L)] and cortisol levels [normal range, 5–25 μg/dL (138–689 nmol/L)] were measured by specific assays (ACTH, immunocytometric assay, Mayo Clinic, Rochester, MN; cortisol, RIA, Diagnostic Products, Los Angeles, CA). Controls were used in the low and high sections of the standard curve. Samples were run in duplicate, and standards were run in triplicate. The intra- and interassay coefficients of variation were both less than 5%. ACTH precursors were measured by a two-site immunoradiometric assay using a pair of antibodies, one that recognizes ACTH and one that recognizes the γMSH sequence in *N*-proopiocortin. Both antibodies are required to produce a signal, and the assay only recognizes POMC and pro-ACTH, but not any of the derived peptides, such as ACTH, *N*-proopiocortin, β-lipotropin, *etc.* The two-site immunoradiometric assay for ACTH precursors enables a direct quantitation of their levels (4, 5).

Laser capture microdissection (LCM)

All adrenocortical tissues were fixed in 70% alcohol and stained with hematoxylin and eosin. Sections were dehydrated in graded alcohol, then in xylene, and were air-dried for 5 min before LCM. The optically transparent thin film caps were placed on top of tissue sections, and the tissue-film sandwich was viewed in an inverted microscope (model CK2, Olympus Corp., Tokyo, Japan). Using a phosphotide laser beam (Arcturus, Mountain View, CA), medullary and cortical cells were separated by melting film and target tissue and removing both from the surrounding area. Total RNA was then extracted from cells adherent to the film cap, in accordance with the RNA microisolation protocol (Stratagene, La Jolla, CA).

RT-PCR

Complementary DNA was synthesized by RT using transfer RNA from the LCM and human pituitary gland mRNA (CLONTECH Laboratories, Inc., Palo Alto, CA) after treatment with deoxyribonuclease I (GenHunter Corp, Nashville, TN). PCR amplification was performed using primers for the following pituitary genes: CYP17, POMC, pituitary homeobox factor-1 (Ptx1), leukemia inhibitory factor (LIF), steroidogenic factor-1 (SF-1), pituitary specific transcription factor-1 (Pit1), prophet of Pit1 (Prop1), prohormone convertase-1 (PC1), and PC2 (Table 1). PCR was performed as previously described (6). All PCR products were verified by sequencing. The negative control was a blank prepared using all reagents with substitution of an equal volume of distilled water for transfer RNA. The negative samples revealed no amplification products.

TaqMan PCR

To quantify the expression of ACTH receptor and CYP17, we applied the TaqMan PCR using the 7700 Sequence Detector (Perkin-Elmer Corp. PE Applied Biosystems, Foster City, CA). Reactions contained 1 $\times$ TaqMan Universal PCR Master Mix, 900 nmol/L forward and reverse primers for ACTH receptor (sense, 5′-CGATCCCACACCAGGAAGAT-3′; antisense, 5′-TCAGTGTGATGGCCCCTTTC-3′) and CYP17α (sense, 5′-CCAGC CGGATCAGTTCATG-3′; antisense, 5′-AAATAGCTTACTGACGGTGAGATGAG-3′), and 200 nmol/L TaqMan probes (ACTH receptor, 5′-TCCACCCTCCCCAGAGCCAACA-3′; CYP17α, 5′-CCCGCTGGATTCAAGAAACGCTCA-3′). 18S primers and probe were added at 50 nmol/L. Thermal cycling proceeded with 50 cycles of 95 C for 15 s and 60 C for 1 min. Input RNA amounts were calculated with relative standard curves for both mRNAs of interest (ACTH receptor and CYP17) and 18S.

Immunohistochemical analyses

Adrenocortical, chromaffin, and immune cells were characterized immunohistochemically in paraffin-embedded sections of adrenal tissue using antibodies against chromogranin A and synaptophysin (clone DAK-A3, DAKO Corp., Hamburg, Germany), CD45 (clones 2B11 and PD7/26, DAKO Corp.), and CD68 (clone KP1, DAKO Corp.), as previ-

TABLE 1. Primer sequences, products size, and primer-specific conditions

Primer	Primer Sequence (5′–3′)	Product (bp)	Cycles	Ta
CYP17				
S	CCAGCCGGATCAGTTCATG	78	40	60
AS	AATAGCTTACTGACGGTGAGATGAG			
POMC				
S	AGTGTCAGGACCTCACCACGGAAA	240	40	65
AS	AGTCTTCGCCCGCTGAGACGTCCTC			
Ptx1				
S	CTAGAGGCCACGTTCCAGAG	439	35	60
AS	CGGTGAGGTTGTTGATGTTG			
SF-1				
S	CGCACGGTGCAGAACAAC	72	40	60
AS	GCGCTGCGTCTTGTCGAT			
LIF1				
S	GTGCAGCCCATAATGAAGGT	398	35	68
AS	CTGGGGTTGAGGATCTTCTG			
Pit 1				
S	TTCTGACGCCTCTGCAACTCT	698	35	68
AS	CAGCCATCCTCATGATCTCTT			
Prop1				
S	AACCAGTACCCCGACATCTG	202	35	68
AS	TGCGTAAGAATAGGGGCAAG			
PC1				
S	AAAACCACCCCAGAAGGTCT	403	30	60
AS	TGTTCTCGTTTGTGGGATCA			
PC2				
S	GACCGGTCTTCACGAATCAT	395	30	60
AS	TTCCCTGTGTATCCCAGCTC			

S, Sense primer; AS, antisense primer; Ta, annealing temperature.

ously described (6). Two antibodies against ACTH were used to determine the presence and distribution of ACTH-positive cells. The presence of ACTH was evaluated by immunostaining with two antibodies to ACTH [NCL-ACTH (clone 56, Novocastra Laboratories, Ltd., Burlingame, LA) and ACTH rabbit IgG antihuman (Sigma, St. Louis, MO)]. Antimouse SF-1 rabbit polyclonal IgG were purchased from Upstate Biotechnology, Inc. (Lake Placid, NY). Bound antibodies were detected by the linked streptavidin-biotin-peroxidase method (DAKO Corp.), and the enzyme reaction was visualized with 3-amino-9-ethylcarbazole (Dianova, Hamburg, Germany) chromogen solution containing 0.05% H_2O_2. All slides were counterstained with hematoxylin for 1 min, rinsed, and mounted. Monoclonal mouse Ig was used as a negative control.

Electron microscopy

For the ultrastructural investigations, small pieces of tissue were fixed in 4% paraformaldehyde-1% glutaraldehyde in 0.1 mol/L phosphate buffer (pH 7.3) for 3 h, postfixed for 90 min in 2% OsO_4 in 0.1 mol/L cacodylate (pH 7.3), dehydrated in ethanol, and embedded in epoxy resin. Ultrathin sections (70 nm) were mounted on 200-mesh uncoated nickel grids. Sections were then stained with uranyl acetate and lead citrate, examined, and photographed at 80 kV under a Phillips electron microscope CM10 (Phillips Electronics, Mahway, NJ).

Results

Histological examination and immunohistochemical characterization

Microscopic examination of the patient's adrenal tumor revealed a well vascularized nodule that contained characteristic adrenocortical adenoma cells. The cells were pale staining and lipid rich, with a cytoplasm that appeared optically clear. There was no diffuse growth pattern, cellular atypical mitotic figure pleomorphism, or other signs of malignancy. The remnant adrenal adenoma cells stained negative for chromogranin A, which was positive in normal adrenal medulla and three specimens of pheochromocytoma. Tumor cells from the patient, however, stained positively for synaptophysin a neuroendocrine tumor marker.

Expression of ACTH protein

The patient's adenoma contained many cells that stained with antibodies to ACTH (Fig. 1D). The staining was similar to that found in normal corticotroph cells of the pituitary (Fig. 1A). In contrast, the normal adrenal cortex and the three other specimens of adrenal adenoma did not stain with an ACTH antibody (Fig. 1, B and C).

Expression of POMC mRNA, CYP17 mRNA, and ACTH receptor mRNA

Adenoma cells were selectively procured by laser capture microdissection with visualization under the microscope, allowing isolation of single cells and cell groups (Fig. 2, A–C). RT-PCR assay for both POMC mRNA and CYP17-α hydroxylase mRNA was performed on the RNA isolated from these cells (Fig. 2D). POMC mRNA and CYP17-α hydroxylase mRNA were expressed in the patient's tumor cells. In contrast, there was no POMC mRNA expression in the normal

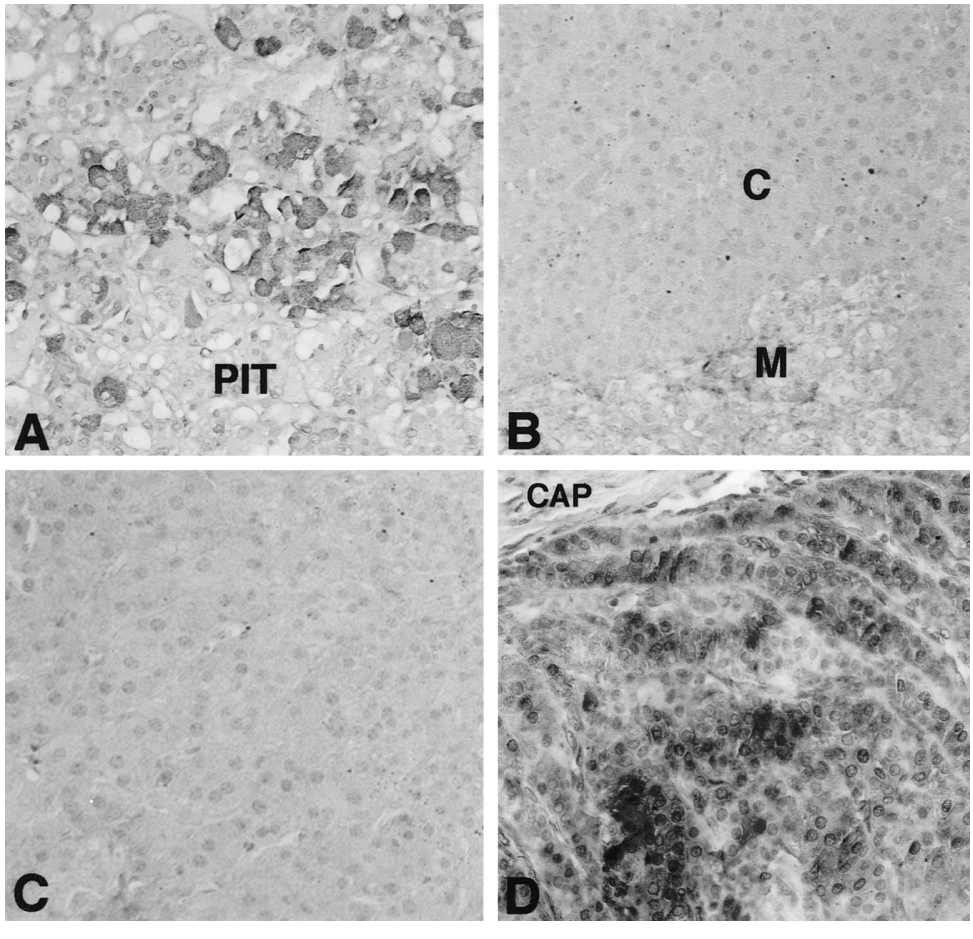

FIG. 1. Immunostaining of specimens of adrenal adenoma, normal pituitary, and adrenal gland. A, Intense immunostaining of corticotroph cells in the normal pituitary, with antibodies to ACTH (×300; reddish-brown staining). In contrast, there was no staining for ACTH in normal human adrenal cortex (B; ×300) or in a representative section of an adrenal adenoma from another patient (C; ×300). The patient's tumor tissue demonstrated heterogeneous intensity of positive staining with anti-ACTH (D; ×300). PIT, Pituitary; C, cortex; M, medulla; CAP, capsule. Immunostaining was visualized with a 3-amino-9-ethylcarbazole chromogen solution.

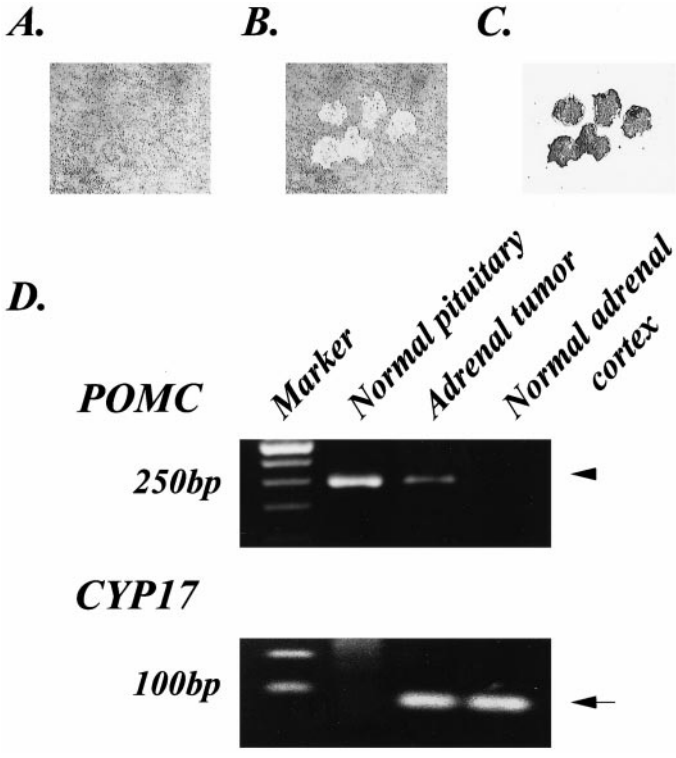

FIG. 2. Laser capture microdissection and RT-PCR of the patient's tumor and control pituitary. Frozen section of the adrenocortical tumor is stained with hematoxylin and eosin (HE; A). Small clusters of the tumor cells were selectively microdissected with the laser (B) and from the isolated tumor cells providing RNA for the expression studies (C). Expression of the POMC and CYP17 gene in pituitary gland, the ACTH-/cortisol-producing adrenal tumor, and normal adrenal cortex (D). The 240-bp (*arrowhead*) and 78-bp (*arrow*) RT-PCR amplification products correspond to the predicted bands for POMC and CYP17. The adrenal tumor expresses both bands for POMC and CYP17. The pituitary does not contain the message for CYP17, and the normal adrenal cortex has no expression of POMC mRNA.

human adrenocortical cells and the three other cortisol-secreting adrenal adenomas, whereas these tissues demonstrated positive expression for CYP17α hydroxylase mRNA. Conversely, pituitary tissue demonstrated no expression of CYP17α hydroxylase mRNA, whereas there was a strong signal for POMC mRNA (Fig. 2D). The expression of CYP17 mRNA and ACTH receptor mRNA was determined by TaqMan PCR. ACTH receptor expression was 115.7 $\pm$ 29.4% in the tumor tissue compared with normal adrenal tissue 101.5 $\pm$ 19.5%. CYP17 expression was 56.3 $\pm$ 3.5% in the tumor tissue compared with 100.4 $\pm$ 14.2% in the normal adrenal tissue.

Ultrastructural analysis

Ultrastructurally, the adrenocortical adenoma cells from controls demonstrated ample SER, lysosomes, and mitochondria characterized by round tubulovesicular cristae (Fig. 3, A and E). Chromaffin cells from normal adrenals and pheochromocytoma cells contained a large number of membrane-bound secretory granules and dense core vesicles of approximately 60–300 nm in diameter (Fig. 3B). These vesicles were either round or elongated. Medium density vesicles and particulate substructure contained epinephrine. Vesicles with electron-dense granules within a large lucent vacuole contained norepinephrine. The cytoplasmic feature of pituitary corticotrophs demonstrated vesicles with highly variable electron density, numerous free ribosomes, and a moderately abundant rough endoplasmic reticulum. The mitochondria were spherical or oval, with laminar or tubular cristae. The secretory granules were numerous in normal pituitaries, but less frequent in a patient with a sparsely granulated corticotroph adenoma (Fig. 3C). The secretory granules demonstrated characteristic variability in size, shape, and electron density, measuring from 150–700 nm. Secretory granules were frequently found in a linear submembrane configuration. In the patient's tumor cells, there were a large number of granules with the characteristic shape and size of pituitary corticotrophs (Fig. 3, D and F). Likewise, the granules lined up in a similar manner to that seen in pituitary corticotrophs. The tumor cells exhibited the round tubulovesicular mitochondria and ample vesicular SER that characterize adrenocortical cells together with the characteristic secretory granules of corticotrophs, all within the cytoplasm of the same cells (Fig. 3F).

Expression of pituitary transcription and differentiation factors and POMC-processing enzymes

The patient's adrenocortical tumor cells and the normal pituitary expressed the mRNA for the Ptx1 (Fig. 4), and SF-1. In addition, both the patient's tumor and the normal pituitary corticotrophs expressed LIF. SF-1 was present in normal adrenocortical tissue, adrenocortical tumors, and normal pituitary. Pit1 and Prop1 transcription factors, important for the differentiation of PRL-, GH-, and TSH-producing cells, were expressed in the pituitary tissue, but not in the ACTH-producing adrenocortical tumor (Fig. 4A). The tumor did not express the enzymes PC1 and PC2 that are responsible for processing POMC to pro-ACTH. Both enzymes were expressed in human pituitary tissue used as a control (Fig. 4B).

Discussion

Our patient's adrenocortical adenoma was an unprecedented clinical challenge. As there was no partial suppression of ACTH levels with dexamethasone, and no response to the CRH stimulator test, ectopic ACTH secretion, rather than Cushing's disease, was suspected. Yet, imaging studies, bilateral inferior petrosal sinus sampling, and adrenal vein sampling suggested an adrenocortical adenoma secreting ACTH and cortisol. Cellular and molecular analyses of the tumor cells revealed the astonishing case of a pituitary-adrenocortical hybrid tumor.

Embryologically, there are a limited number of patterns in the development of the HPA axis. The adrenocortical primordium is derived from mesenchymal tissue contiguous with the coelomic epithelium of the suprarenal cavity, near the urogenital ridge (7, 8). On the other hand, adrenomedullary cells appear in the adrenals of fetuses by migration of sympathogonia from the primitive sympathetic ganglia adjacent to the adrenals (7, 8). This embryonic development explains the morphogenesis of adrenal rest tissue in the gonads and the intermingling of cortical and chromaffin tissue

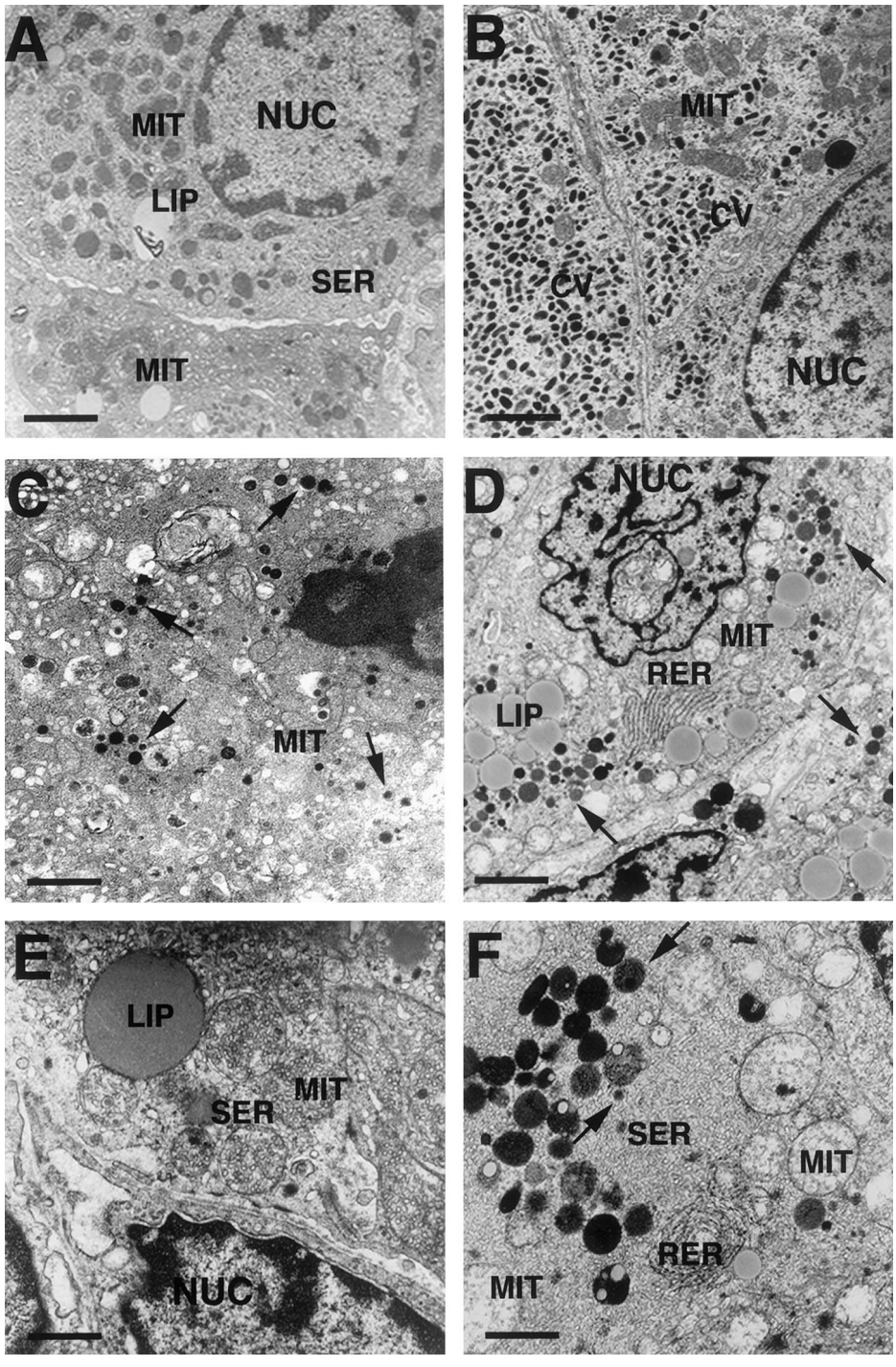

FIG. 3. Electron micrograph of normal human adrenal cortex (A and E), medulla (B), pituitary corticotroph adenoma (C), and the patient's tumor (D and F) stained with uranyl acetate and lead citrate. Compared with normal human adrenals (A), the patient's adrenocortical tumor cells (D) contain numerous secretory granules (*arrows*) and rough endoplasmic reticulum (RER). The secretory granules (*arrows*) exhibit the characteristic size, shape, and electron density observed in a sparsely granulated corticotroph adenoma (C). These secretory granules differ from the chromaffin vesicles (CV) that are abundant in the cytoplasm of chromaffin cells (B) and are either round or elongated, membrane-bound, dense core vesicles. In addition, the patient's tumor cells contain the characteristic round mitochondria (MIT) with vesicular internal membranes, the typical vesicular and tubular SER, and lipid droplets (LIP) seen in other adrenocortical adenoma cells (E). NUC, Nucleus. *Bar*: A–D, 3 μm; E and F, 0.8 μm.

within normal adrenal glands (9, 10). Interestingly, even normal human adrenocortical cells may exhibit properties of neuroendocrine cells (11), whereas various adrenocortical tumors aberrantly express neuroendocrine markers and/or receptors for neurotransmitters, neuropeptides, and cytokines (6, 12–14). In patients with primary pigmented nodular adrenal disease, we found expression of synaptophysin, and on the ultrastructural level, these cells had vesicle-like secretory granules (15). Our patient's adrenal tumor, in addition to synaptophysin expression, produced large amounts of ACTH precursors that cross-reacted in the ACTH assay, and the tumor also contained secretory granules usually found in pituitary corticotrophs (16). Similar to a pituitary corticotroph tumor and in contrast to pheochromocytomas or other neuroendocrine tumors, the cells did not express the neuroendocrine tumor marker, chromogranin A (17). The ACTH released into the circulation consisted of less active ACTH precursors (4, 5), which apparently did not provide adequate stimulation to the contralateral side, explaining the atrophy of the left adrenal and the remnant right adrenal cortex in our patient. Quantitative TaqMan PCR of CYP17 mRNA and ACTH receptor mRNA did not reveal any sig-

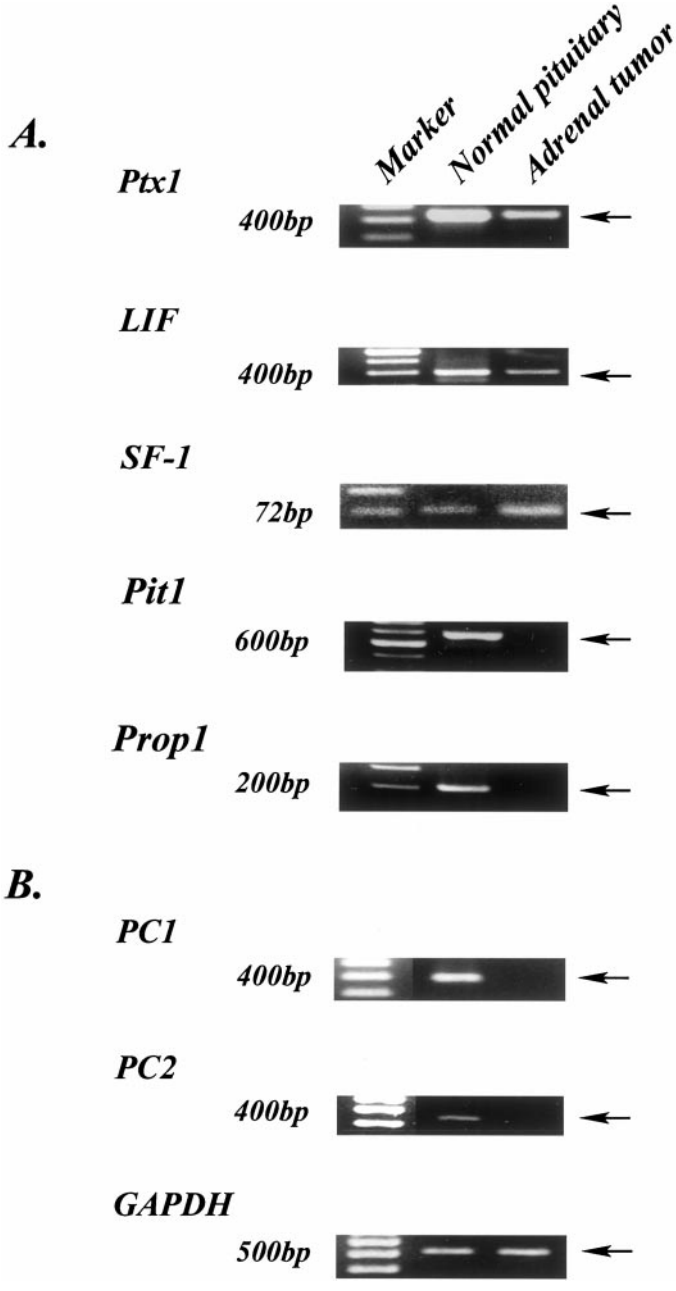

FIG. 4. RT-PCR analysis of human pituitary and the adrenal tumor mRNA. Human pituitary gland expresses Ptx1 (439 bp), LIF (398 bp), SF-1 (72 bp), Pit1 (698 bp), and Prop1 (202 bp) mRNA (A) and POMC-processing enzymes, PC1 and PC2 (B). PCR-amplified products of PTX-1, LIF, and SF-1 are shown in the adrenal tumor of the patient.

nificant changes compared with normal adrenal tissue. The expression of PC1 and PC2, the enzymes processing POMC peptides to ACTH, was negative in the patient's tumor, providing further evidence that only ACTH precursors were released from the adrenal adenoma. Therefore, these data suggest that the ACTH precursor produced locally in this tumor did not exhibit a significant autocrine/paracrine action and do not explain the autonomous hypersecretion of cortisol.

The pituitary gland is derived from the oral ectoderm of the dorsomedial region of Rathke's pouch and from an evagination of the infundibular portion of the diencephalon of the brain (16, 18, 19). Therefore, an intermingling of the centrally located ectodermally derived anterior pituitary tissue with the mesodermally derived adrenocortical tissue in the periphery should not be expected. Yet here we demonstrate that this can occur in humans, possibly revealing a hitherto unrecognized plasticity within the human HPA axis. Pituitary development and differentiation are regulated by the interaction of multiple transcription factors (19–21). These factors regulate pituitary lineage and commitment with their expression pattern, allowing recognition of progenitor cells from which particular tumors are derived (22). Recent evidence suggests that a similar code of transcription factors and *trans*-activators may regulate differentiation and gene expression in the adrenal and pituitary (23–26). Thus, SF-1 is both a key transcription factor for the development of adrenal, gonadal steroidogenic tissue, and the pituitary (24–26). Likewise, Nur77, which belongs to the nuclear receptor family, is expressed at all three levels of the HPA axis (23). It activates transcription of the POMC gene in the pituitary and mediates ACTH-induced expression of steroidogenic enzymes in the adrenal cortex. Ptx1, a bicoid-related vertebrate homeobox gene, is a strong activator of several pituitary-specific promoters and is considered a pan-pituitary transcription factor. This is the first report describing the presence of this pituitary transcription factor in adrenal tissue. Ptx1 achieves cell- and promoter-specific transcriptional activation by cooperation with lineage-restricted transcription factors and growth factors (24). Thus, the combined expression of Ptx1 and LIF, a cytokine required for the differentiation of corticotrophs, has been implicated in the formation of ACTH-producing pituitary tumors (27, 28). Similarly, in our patient's tumor both factors were expressed, whereas other pituitary transcription factors, such as Pit1 and Prop1, which are involved in the formation of lactotrophs, thyrotrophs, and somatotrophs, were absent (22). ACTH is the earliest intact human hormone to be secreted (29). Furthermore, the commitment of the POMC-secreting cell appears to occur in a cell lineage independent of the other pituitary trophic hormone-secreting cells and may reflect the possibility that an independent POMC-expressing cell may arise in the periphery. This intriguing possibility is also supported by the observation that POMC-expressing cells are most resistant to pituitary radiation or compression. The clinical, morphological, and molecular features of this case suggest a hitherto unrecognized genetic and phenotypic plasticity within the human HPA axis.

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